We Need Expanded Newborn Screening

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COMMENTARY

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For many conditions, when newborn screening detects an abnormality that can be effectively treated, it can make the difference between a healthy life and one that requires long-term care. For this reason, the World Health Organization in 1998 recommended that newborn screening be mandatory and free of charge when early diagnosis and treatment could benefit children.[1] Carlson recently commented that "newborn screening represents one of the major child health advances of this past century."[2] Those of us who have cared for infants affected with conditions for which screening has been introduced would agree heartily with this comment. Our ability to identify affected newborn infants, when totally asymptomatic, and institute programs and treatments that prevent serious morbidity and mortality is a great privilege for the pediatrician. A core of our specialty is preventive medicine, such as the practice of the careful evaluation of infants through weight and measurement in an effort to detect and treat serious underlying medical conditions.

BACKGROUND

Newborn screening for serious metabolic disorders is one of the most dramatic of our preventive pediatric measures. More than 40 years ago a special diet was developed for phenylketonuria (PKU), a rare metabolic condition; it has dramatically improved the outcomes of these infants when the diet is initiated early in infancy. A simple screening test was developed by Guthrie using dried blood spots—a system that is still at the core of newborn screening today.[3] After enormous advocacy by both professional and parent groups, newborn screening was adopted widely throughout the developed world. When newborn screening for PKU started, there were many unknowns about PKU, including maternal PKU. There were some adverse outcomes during this learning period, almost always reversible, as clinicians and scientists learned the spectrum of the disease and how best to treat these children.[4,5] Technologic changes also occurred, specifically, the ability to measure accurately serum phenylalanine concentrations and thereby prevent phenylalanine deficiency during dietary management. These adverse effects have been dramatically emphasized by those who have been opposed to expanded newborn screening.[6] Since the very beginning of newborn screening for PKU, there has been controversy about a wide variety of issues; those concerns are very similar to those expressed today about expanded newborn screening. A particular concern, about legislation (as well as other issues) and newborn screening, was reviewed in this journal 40 years ago by Bessman.[7]

Atkins et al have noted the struggle of policy makers who must deal with medical issues that are the subject of scientific debate. I agree with their conclusion that "on closer examination, many of these debates are manifestations of conflicting perspectives and values as much as disagreements over the evidence."[8]

As we survey the first 40 years of newborn screening for PKU, we see a consistent learning experience about the condition, such as the discovery of maternal PKU, but we have a whole generation of young adults with treated PKU who have normal intelligence and are pro-

Abbreviations: PKU, phenylketonuria; MS/MS, tandem mass spectrometry; HRSA, Health Resources and Services Administration; ACMG, American College of Medical Genetics; MCAD, medium chain acyl-CoA dehydrogenase

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ductive members of society. Without this early treatment, these children would have overwhelmingly suffered profound mental retardation, which characterizes untreated PKU.[9] Indeed, one of the active members of the National Institutes of Health Consensus Development Conference on PKU[9] was a young college student, who herself had early-detected and treated PKU. Recently, Hardelid and Dezateux[10] reviewed the robust evidence that early diagnosis of PKU, through neonatal screening, when combined with access to appropriate treatment and follow-up, represents a highly successful public health intervention to prevent severe neurologic morbidity.

In addition to PKU, currently screened for in all states, a variety of other tests are now being performed. Newborn screening for hypothyroidism is widely performed today, and the benefit from detecting and treating infants with this condition is enormous. In a study recently reported from France, these patients' school achievements were similar to those of the general population in obtaining the French high school diploma, which strongly validated the newborn screening for congenital hypothyroidism.[11] Similarly striking results are obtained with newborn screening and treatment of biotinidase deficiency, a rare recessive disorder. In a study by Weber et al,[12] no child with profound biotinidase deficiency, which was detected by newborn screening ($n = 25$) and treated with biotin supplementation, had auditory or visual loss, and milestones of speech development and motor skills were reached at an appropriate age. This contrasted sharply with infants who had this deficiency and were not detected and treated in the newborn period.

Over the past few decades, new technology has permitted the testing of newborn infants for conditions that could not have been practically detected in the past. The most visible of these technologies is tandem mass spectrometry (MS/MS), which permits the accurate determination of dozens of compounds on a single, speedy analysis in a public health setting using the traditional dried blood spot.

Newborn screening is a public health program that in all instances is the responsibility of state health departments. Because these are state programs, there has been and continues to be considerable variation from state to state. The addition of new conditions to be tested for in the various states has been driven by a variety of forces. Most states have advisory committees that, not surprisingly, reach independent decisions about the conditions that are appropriate for newborn screening.

The considerable variation from state to state as far as what conditions are included in the newborn screening panel has been a significant issue and remains so even today. The National Newborn Screening Network maintains an excellent database of the tests currently performed by the various states.[13] The advent of MS/MS, as well as increasing advocacy of the families of affected individuals and medical experts, have been strongly driving the expansion of newborn screening. This rapid expansion has made discrepancies among the states even more dramatic.

EXPANDING NEWBORN SCREENING

Against this background, the Health Resources and Services Administration (HRSA) awarded a contract to the American College of Medical Genetics (ACMG) to convene an expert group and panel to examine newborn screening. There were several aspects to this contract, but the core mission was to examine conditions amenable to newborn screening, devise mechanisms for adding conditions to the newborn screening panels, and recommend a panel of conditions appropriate for newborn screening. This expert group, and its various panels and subgroups, worked nearly 2 years on this project. The group(s) consisted of physicians, medical (and especially metabolic) geneticists, laboratorians, consumers, public health experts, health policy and health economists, lawyers, and medical ethicists. All of the involved federal agencies served on the groups. This is one of the largest, most diverse (and expert) groups that has examined the issue of newborn screening up to this time.[14]

This group has formally recommended to the HRSA that infants be screened for 29 conditions.[14] All of the conditions on the "core-conditions" list are felt by the leading experts to have a beneficial treatment if identified early. MS/MS, the powerful technology that permits the identification of many compounds with great accuracy on a single run using dried blood spots, is required for detecting many of these recommended conditions. During the course of detecting these 29 core conditions in the laboratory using MS/MS, a considerable number of other conditions, not as well known as those on the core panel, are identified. These conditions have been noted as "secondary conditions" by the ACMG expert panel. In virtually every instance, the compounds listed as secondary conditions must be considered in making the diagnosis of a core condition. It was the recommendation of this expert panel that these secondary conditions (25 of them) also be reported. It was strongly felt that if there was such an abnormality present, then whatever information was known about this condition should not be kept secret. This is in stark contrast to the recent recommendations of the German screening program, in which information about conditions not listed on their panel would not only be withheld but that the information should be destroyed.

Lay journalists have cast these recommendations as causing great debate within the United States.[15] Some of those opposed to expanded screening have presented remarkable comments about the problems with PKU screening in the early years. For example, "it turned out that 95% of people with an abnormal screening test had

no disease, and it turned out that the diet was lethal. It caused brain damage in we don't know how many kids."[15] One of those clinicians/scientists involved in newborn screening since its inception is aware of some adverse outcomes, indeed, but in remarkably few patients over the past 40 years (S. Snyderman, MD, personal communication, 2005). This is consistent with my own personal experience, as well as the data in the literature.

The article by Botkin et al in this issue of *Pediatrics*[16] presents many of the concerns about expanded screening, and we must continue to examine and consider each of these as we move forward.

The entire infrastructure needed for expanded newborn screening programs is certainly not in place; this is widely and well recognized. However, I feel that it would be unwise, indeed unethical, to deny life-saving and simple treatments to infants when simple and accurate tests are currently available. Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is an excellent example of such a situation.

I remain somewhat surprised that some do not appreciate the issues surrounding the lack of controlled trials in therapy of some of the potentially fatal conditions. It is important, for example, to look at MCAD deficiency. This is one of the most common defects of mitochondrial β oxidation, and it is clear that careful avoidance of fasting, a remarkably simple treatment, can be life-saving in some infants. Recently, researchers in the Netherlands[17] performed a population-wide clinical and epidemiologic study that identified 155 patients (from 110 families) who were born before 2003 and had MCAD deficiency. Most children presented acutely during infancy; 22% of those who presented acutely died! In the 27 children who died, 9 were identified as having the disorder only after a later-born proband was diagnosed; 1 or more clinical admissions preceded the diagnosis in 25 cases. Within Australia, a preliminary report has compared the outcomes of screened and unscreened infants with MCAD deficiency.[18] In that setting, 6 of 37 unscreened infants who presented clinically died, which represented 21% of those who presented clinically. In the screened cohort, only 1 has died (on day 3 before test results were available). However, 3 of the screened infants suffered decompensation episodes, although most had prophylactic admissions. Obviously, with such clear data indicating that a significant portion of infants with MCAD deficiency suffer fatal decompensations, no prudent physician would fail to provide treatment information to such families if the condition had been identified.

There is little advantage at this time to discuss whether there should be expansion of newborn screening; it is occurring briskly at this very moment. Decisions to expand newborn screening are being made by various groups throughout the world. Indeed, according to the National Newborn Screening and Genetics Resource Center Web site, the majority of infants in the United States are already being tested for an "expanded panel" of conditions, which includes many of those detected by MS/MS.[13] Indeed, most of the developed world is also rapidly expanding their newborn panel; the Dutch Ministry of Health recently decided to follow the advice of the Dutch Health Council to expand their current program to include 18 conditions, up from their current 3.[19]

As we move forward with expanded newborn screening, there are enormous needs in infrastructure. I will discuss only a few of the important ones that need to be addressed promptly.

Confirmatory Diagnosis, Follow-up, and Treatment

A significant issue that presents when a diagnosis of a very rare condition is suggested by a positive screening test is the mechanism for immediate follow-up and confirmation of such a diagnosis. The facilities vary widely for such follow-up around the country, and it is incumbent on the state programs to work in their regions to provide follow-up support in terms of funding and organization. An important effort along these lines is the recently funded HRSA Regional Genetics and Newborn Screening Collaborative groups.[20] These collaborative groups, which include all of the states and territories, were organized in an effort to provide regional and national expertise in assisting with the diagnosis and follow-up of rare conditions. A national coordinating center for this group has been funded to bring together people with various expertise throughout the country. Within these regional collaborative groups, there are many programs underway to enhance our infrastructure for newborn screening. For example, an important program in region 4 is a training effort for the mass spectroscopists from the various states to ensure excellence in the laboratory aspect of the newborn screening system. This training takes place in one of the most expert laboratories in the world, which is located within region 4. Other training programs have also been conducted at other sites around the country.

Shortages of Experts

There is a recognized shortage of experts in the area of biochemical genetics. This issue has not been solved but has been under discussion by the major professional groups, and at least 2 important new initiatives are currently underway. Both the Society for Inherited Metabolic Diseases and the ACMG have announced new fully funded fellowships for training in these areas to be awarded this upcoming academic year. This clearly won't solve the problems, but it certainly begins to address this issue.

The Issue of False Positives

Within the screening community, there is great concern about the frequency of false-positive results. When we

screen for so many conditions, it is absolutely critical that we keep the number of false positives at an absolute minimum while ensuring that no infant with true disease for which the screening is done is missed.[21] If there are frequent false positives, a true positive can readily be overlooked. The laboratories are truly focusing on this area. In addition to the excellent work on cutoffs for mass spectroscopy,[22] the introduction of secondary tests for such conditions as hereditary tyrosinemia is invaluable.[23] The number of false-positive screening tests can, indeed, be kept low.

Education of the Profession, the Patients, and the Public

It is an extremely challenging problem to devise and provide education about a series of rare and complex diseases to the profession, the patients, and the public. These are long-term issues, and we will need to include, at a minimum, increased educational efforts within our medical schools and our residency training programs, increased public awareness, and, importantly, the availability of information in a readable, understandable format on very short notice. There are many efforts underway in this area, and I will comment on just a few. The National Library of Medicine has placed on its Web site some excellent new material dealing with the conditions that are on the recommended panel presented by the ACMG expert panel.[24] These brief documents will provide immediate readable information for widespread use and discussion. The ACMG has developed a series of outstanding materials for primary care physicians. These "act sheets" are brief documents that explain the conditions succinctly but expertly. In addition, there are fact sheets that convey information about the conditions and, importantly, a diagnostic algorithm document for each condition. All of these documents are on the ACMG Web site.[25] These materials have been prepared by experts in each of the conditions under discussion and provide short but expert advice about how to proceed in the event that a presumptive positive screening test is reported. Connection to more extensive information and advice is a part of all of these sheets.

Informed Consent

Informed consent will need continuing and extensive evaluation and research. For PKU, screening tests are mandated by state laws in most instances, and the diagnosis and treatments are of clear benefit to the child. Under these circumstances, informed consent is obtained from families in only a few states. In some of the less-well-understood conditions, most feel that informed consent is not only desirable but should clearly be obtained. However, obtaining such consent is not an easy issue. For example, how does one adequately explain the array of tests being performed and the various potential outcomes of either accepting or refusing such testing?

New Technologies and Treatments

With increased interest in newborn screening, I feel it is quite likely that the number of conditions screened in the newborn period will expand greatly beyond the currently recommended conditions. There are a series of conditions for which emerging or already-known effective treatments have been devised. The extraordinarily good results with very early bone marrow transplantation in infants with severe combined immunodeficiency is an excellent example.[26] The very early treatment of infants with Krabbe disease (identified early because of family history) with umbilical-cord blood transplants has demonstrated dramatic improvement.[27] The first recognized lysosomal storage disease, infantile Pompe disease, which is routinely fatal in early infancy, has shown dramatic results with enzyme-replacement therapy. Such therapy is under consideration for approval.[28] These conditions will clearly be under early discussion for newborn screening. Other lysosomal storage diseases, as well as peroxisomal disorders, have available treatments that require very early diagnosis for optimal treatments.

There are a number of other disorders such as spinal muscular atrophy and Duchenne muscular dystrophy for which clinical trials are underway that, if effective, will require careful consideration for newborn screening. As successful treatments for these important diseases emerge, early treatment will be essential, and the only way that this can be done is to have very early diagnosis. Because these conditions usually occur in families in which there is not a family history, newborn screening—requiring the development of accurate, sensitive, and practical tests suitable for the public health sector—is the only practical avenue for early diagnosis.

Some of the conditions for which screening has been underway for a very long time would benefit greatly from having new and simpler forms of treatment (eg, PKU). In response to these needs, the National Institutes of Health recently released 2 documents requesting grants related to new technologies suitable for newborn screening, as well as for new treatments for screenable diseases.[29,30] Certainly some of the long-treated diseases, such as PKU, would benefit greatly from a simpler therapeutic regime.

Under discussion is the possibility of screening for conditions that are outside the conventional area of newborn screening. These are conditions for which the treatments are not special diets or even enzyme replacements or stem cell transplants but involve efforts such as early intervention to improve eventual outcomes. The best example of this situation is that of the fragile X syndrome, for which studies are underway to evaluate the potential benefits of early intervention, as well as issues surrounding informed consent and the public's reaction to newborn screening for such conditions.[31]

It is clear to me that newborn screening programs will

likely to continue to add additional conditions, and the benefits from detecting treating serious, and at times fatal, disorders will continue to expand. We must be aggressive in working on the enormous infrastructural needs that are required for such programs and be aware of the many areas in which we need additional information but focus on the enormous benefit that our infants derive from carefully performed newborn screening.

A question that always arises has to do with the cost of newborn screening. Although it is difficult to calculate the total costs of all the programs surrounding newborn screening, it is rather easy to calculate the direct laboratory costs and immediate follow-up, which are somewhat over $100 per infant screened. Because we screen 4.1 million infants yearly in the United States, this would translate into approximately $410 000 000 in annual expenditures on newborn screening programs—a great deal of money indeed. If, however, one examines the expenditure of our developed country on other health issues, it is clear that the cost for the newborn screening program is less than 1 month's investment in a single drug used for treating hypercholesterolemia.[32] Sales of this most popular single drug were reported at $1 000 000 000 per month.

CONCLUSIONS

Although we are appropriately spending a great deal of time and effort examining the current expansion of newborn screening, it is my belief that we are at the beginning of an even greater period of expansion. There has not been a systematic look at screening newborn infants for infectious diseases: what might be screened and what would be the value of such screening. The ACMG/HRSA report did not examine infectious agents.

There are conditions that do not fit with our traditional newborn screening programs using dried blood spots; this will likely require the expansion of our newborn screening programs to increasingly using on-site programs to screen for important, treatable conditions. One such group of conditions is already on most state newborn screening panels and can be detected with newborn hearing testing. There are a number of situations that likely require routine newborn screening that will take place in the nursery, not unlike the situation that occurs today with newborn screening for hearing difficulties. A significant problem today in pediatrics surrounds the serious complications that result from hyperbilirubinemia. Efforts are underway to identify newborns at risk for significant hyperbilirubinemia that might well require routine bilirubin determinations in the nursery.[33] However, there is the issue of how we can develop tests for all newborns that will reliably identify and prevent serious problems related to bilirubin toxicity. There is increasing scientific evidence about the potential value of routine screening of all infants with such techniques as pulse oximetry to detect serious, potentially fatal, congenital heart disease. Also, as has frequently been the case in newborn screening, specific examples of infants who have died as a result of disorders that could have been identified by newborn screening and successfully treated are highly visible and point to their importance in developing newborn screening policy.[34]

There are important conditions, such as Wilson disease, that cannot be reliably detected on newborn dried blood spots (with current techniques) but for which effective and potentially life-saving treatments exist. Effective screening can be done in later infancy, but such screening would require additional thought about the timing of certain screening tests. Thus, there are not only additional conditions to consider in the newborn period but also issues related to potential changes in the nature and organization of some of our newborn screening programs.

Many families feel very strongly that they would have benefited greatly from knowing in early infancy the nature of their child's problem although there might not be a specific treatment. With conditions such as fragile X syndrome, the early introduction of special intervention programs could well prove extremely valuable in the long run; studies are underway to assess such programs. Families feel that even in the absence of such specific benefit they still would benefit from avoiding the diagnostic odyssey that can go on for years and be very expensive and time consuming, all while they are fully aware that there is something with their infant that is outside the normal range. The evolving technologies will permit us to add additional tests to the screening panel at little additional cost. However, they should not be added unless there is a specific benefit to either the child or the family from having this early information.

I think it is very likely that we are at the beginning of the expansion of newborn screening, with many new screening tests and treatments on the horizon that will be helpful and potentially life-saving to our infants.

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